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Synthesis and Reactions of Some Azolecarboxylic Acid Derivatives

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Reaction of several azoles with phosgene or triphosgene was studied. Besides benzotriazole (previously described reaction), only indazole, 5-nitroindazole and 5-methylbenzotriazole gave the corresponding 1-azolecarbonyl chlorides **1a-d**. Azoles of weak acidity (imidazole, 1,2,3-triazole, 1,2,4-triazole, benzimidazole) could not give stable acyl chlorides, while strong acidic azoles like tetrazole and 4,5,6,7-tetrachlorobenzotriazole did not react at all. Chlorides **1b-d** readily reacted with alcohols, amines, amino acids and their esters like the previously described 1-benzotriazolecarboxylic acid chloride (**1a**), giving 1-azolecarboxylic acid esters (**2**) or amides (**3**), *N*-(1-azolecarbonyl)amino acids (**4**, **5**), their esters (**8**, **9**) or amides (**10**, **11**). However, a significant difference was observed in the reactivity of azole derivatives **2–11** with amines, alcohols and *N*-protected amino acids or in their stability in acidic and basic aqueous media. Benzotriazole and methylbenzotriazole derivatives were more reactive than indazole or nitroindazole derivatives. The higher reactivity was in correlation with the shift of the IR carbonyl absorption band to higher wave numbers.

INTRODUCTION

After successful synthesis of 1-benzotriazolecarboxylic acid chloride (BtcCl, **1a**)¹ and its application in syntheses of numerous carbonic acid derivatives and other compounds,^{1–16} some open questions have still remained unsolved and the answers are elucidated in this paper.

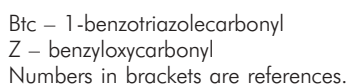
Staab and collaborators studied the reactions of phosgene with azoles (pyrazole, imidazole, triazole and their benzo condensates) and the reactivity of thus prepared 1,1'-carbonyldiazoles. Their results have been published in several papers and are summarized in a review article.¹⁷ 1,1'-Carbonyldiimidazole has proved to be the best among carbonyldiazoles and it is nowadays a commercially available compound widely used in synthetic organic chemistry.

In our search for a new method for the preparation of pharmacologically active carbamates,^{1–3} we found that benzotriazole (an industrial product) reacted with phosgene and quantitatively gave BtcCl of stability comparable to that of other carboxylic acid chlorides. The compound was then applied in syntheses of numerous products (Schemes 1 and 2).

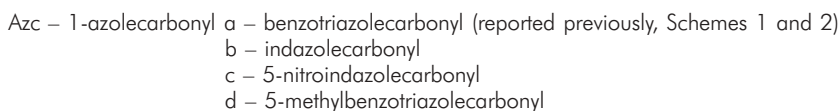
Other authors^{17,18} accomplished the phosgenization reaction with azole/phosgene mole ratio 2:1 in the presence of triethylamine (TEA) as hydrogen chloride acceptor. On the other hand, benzotriazole (BtH) reacted with phosgene excess, affording BtcCl and hydrogen chloride, which was evaporated under reduced pressure.^{1,9} Under the same reaction conditions, more basic azoles (imidazole, 1,2,3- and 1,2,4-triazole, benzimidazole) gave unstable

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Scheme 2.



Bzl – benzyl
Me – methyl
Z – benzyloxycarbonyl

Scheme 3.

indazole, 5-methylbenzotriazole and 4,5,6,7-tetrachlorobenzotriazole. Phosgenization of the azoles was performed in an analogous way to phosgenization of benzotriazole⁹ by heating the corresponding azole in 20 % phosgene solution in toluene, 1–2 h at 80–90 °C. Under these reaction conditions, besides benzotriazole, only indazole (InH), 5-nitroindazole (NInH) and 5-methylbenzotriazole (MBtH) gave the stable corresponding 1-azolecarbonyl chlorides (AzcCl, **1a-d**) (Table I). As it was shown previously,¹ the azoles of weak acidity (imidazole, 1,2,3-triazole, 1,2,4-triazole, benzimidazole) could not give stable acyl chlorides, while strong acidic azoles like tetrazole and tetrachlorobenzotriazole, with pK_a values similar to acetic acid, did not react at all. Staab reported, without any experimental data, that silver tetrazole salt and phosgene gave a mixture of tetrazole and carbonyl ditetrazole.²³

In order to avoid complicated handling and dosing with toxic gaseous phosgene or phosgene solution, analogous syntheses of chlorides **1a-d** were performed with solid triphosgene. It was shown that phosgene could be successfully replaced by triphosgene:



The reactions proved to be safer and more simple. In addition, only 1/3 mole of triphosgene was required. The reactions proceeded successfully at room temperature in the presence of triethylamine (TEA) or some other tertiary amine, while reflux in toluene and 20 % excess of triphosgene were needed in amine-free reactions.

IR spectra of the prepared chlorides **1a-d** were recorded. The main $\nu(\text{CO})$ absorptions could be found in the range from 1735 to 1765 cm^{-1} (see Table I). Besides, two weak absorption bands were present at higher and lower wave numbers. For example, $\nu(\text{CO})$ of BtcCl was at 1795w, 1765s and 1716w cm^{-1} . It was shown that the higher reactivity of azole derivatives (Table IV) was in correlation with the shift of the $\nu(\text{CO})$ absorption band to higher wave numbers. These results were in agreement with previous findings for the 1-carbonyl and 1-acyl azoles.¹⁷ The position of CO group in **1a** and **1b** was confirmed earlier.^{1,24,25} **1d** showed the $\text{N}=\text{N}$ absorption band at 1600 cm^{-1} , characteristic of 1*H*, and no $\text{C}=\text{N}$ absorption at 1540 cm^{-1} , characteristic of 2*H* benzotriazole. IR spectrum of **1c** was almost identical with the spectrum of **1b**, which was previously confirmed as 1*H* derivative.

Better stability of chlorides **1a-d** in comparison with carbonyl diazoles could be seen even during the preparation of samples for IR spectroscopy. For example, 1,1'-carbonyl -diimidazole or -diazotriazole decomposed to the corresponding azole and carbon dioxide if the smallest amount of moisture was present in KBr pellets.²³ In contrast, chlorides **1a-d** gave identical spectra in KBr and nujole, without any sign of the hydrolysis product.

Reactions of BtcCl (**1a**) and its derivatives have been reported in a number of papers^{1–16} and are summarized

in Schemes 1 and 2. Some of the published data were used in this paper for comparison. Reactions with chlorides **1b-d** occurred in an analogous way to those with **1a** (Scheme 3). With methanol they gave methyl esters **2a-d**, with cyclohexylamine the corresponding amides **3a-d**, and with amino acids glycine (Gly) or phenylalanine (L-Phe) *N*-(1-azolecarbonyl)amino acids (**4a-d**) and (**5a-d**), respectively. *N*-protected amino acids **4** and **5** were subsequently converted to the corresponding chlorides **6a-d** and **7a-d** by means of thionyl chloride and further to esters **8a-d** or **9a,b** or cyclohexylamides **10a-d** or **11a**. Esters **8** and **9** were also prepared by the reactions of amino acid ester hydrochlorides **14** and **15** and chlorides **1a-d** in the presence of *N*-methyl morpholine (NMM) as hydrogen chloride acceptor. Tables II and III give the reaction conditions and characterization data of the synthesized compounds.

Described reactions proceeded mainly at room temperature in high yields. Chlorides **1b-d** readily reacted with alcohols, amines, amino acids and their esters, as previously described for BtcCl (**1a**). However, a significant difference was observed in the reactivity of thus prepared products in comparison with benzotriazole bearing compounds. Benzotriazole and methylbenzotriazole derivatives were more reactive than indazole or nitroindazole derivatives. For example, reactions of azole carboxylic acid esters **2** with cyclohexylamine were finished practically immediately (**2a** and **2d**), in 7 h (**2c**) or in 20 h (**2b**), depending on the azole moiety. Indazole and nitroindazole carboxylic acid amides **3b** and **3c** similarly showed low reactivity with cyclohexylamine. They reacted only at a high temperature (155 °C), after dissociation to the corresponding azole and isocyanate $\text{C}_6\text{H}_{11}\text{NCO}$. This was confirmed by the heating of compounds **3b** and **3c** in *N,N*-dimethylformamide (DMF) at 155 °C. Liberated cyclohexyl isocyanate was absorbed in DMF solution of cyclohexylamine and transformed to dicyclohexyl urea (DCU, **13**). On the other hand, benzotriazole and methylbenzotriazole derivatives **3a** and **3d** quantitatively gave DCU in a nucleophilic substitution reaction, in a one day-period at 20 °C or in a few minutes at 80 °C.

Similar behaviour was observed in reactions of *N*-(1-azolecarbonyl)-L-phenylalanine derivatives **5a-d** with methanol. Compounds **5a** and **5d** reacted at room temperature and gave L-phenylalanine methyl ester (**24**) through the *N*-carboxy anhydride (NCA) (see pages 229–233),³⁰ **5c** gave only traces of the same ester, while **5b** remained unchanged after 7 h of heating at 60 °C.

Reactions of *N*-(1-azolecarbonyl)glycine methyl esters **8a-d** with Z-L-Phe-OH (Z – benzyloxycarbonyl) were studied as well. In these reactions, a peptide bond between *N*-activated amino acid derivatives **8** and *N*-protected amino acid (Z-L-Phe-OH) was formed, affording dipeptide derivative **16**.¹⁵ After heating the reaction mixture of Z-L-Phe-OH with **8b** or **8c** for 15 h at 140 °C, the reaction proceeded partially (product **16** was detected by

TABLE II. Preparation of azolecarboxylic acid derivatives

	Reactants	Solvent	<i>T</i> / °C	<i>t</i> / h	Yield / %	Product
Indazole series						
IncCl (1b)	MeOH	methanol	20	1	98	IncOMe (2b)
IncCl (1b)	C ₆ H ₁₁ NH ₂ / TEA	benzene	20	1	94	IncNHC ₆ H ₁₁ (3b)
IncCl (1b)	Gly	dioxane	20	20	52	Inc-Gly-OH (4b)
IncCl (1b)	L-Phe	dioxane	20	20	90	Inc-L-Phe-OH (5b)
Inc-Gly-OH (4b)	SOCl ₂	SOCl ₂	20	20	100 ^(a)	Inc-Gly-Cl (6b)
Inc-L-Phe-OH (5b)	SOCl ₂	SOCl ₂	20	20	100 ^(a)	Inc-L-Phe-Cl (7b)
IncCl (1b)	H-Gly-OMe · HCl / NMM	dioxane	20	2	63	Inc-Gly-OMe (8b)
IncCl (1b)	H-L-Phe-OBzl · HCl / NMM	dioxane	20	2	41	Inc-L-Phe-OBzl (9b)
Inc-L-Phe-Cl (7b)	BzlOH / TEA	benzene	20	0.75	81	Inc-L-Phe-OBzl (9b)
Inc-Gly-Cl (6b)	C ₆ H ₁₁ NH ₂ / TEA	benzene	20	0.75	83	Inc-Gly-NHC ₆ H ₁₁ (10b)
Nitroindazole series						
NIncCl (1c)	MeOH	methanol	20	1	79	NIncOMe (2c)
NIncCl (1c)	C ₆ H ₁₁ NH ₂ / TEA	benzene	20	1	79	NIncNHC ₆ H ₁₁ (3c)
NIncCl (1c)	Gly	dioxane	20	20	97	NInc-Gly-OH (4c)
NIncCl (1c)	L-Phe	dioxane	20	20	71	NInc-L-Phe-OH (5c)
NInc-Gly-OH (4c)	SOCl ₂	SOCl ₂	75	1	100 ^(a)	NInc-Gly-Cl (6c)
NIncCl (1c)	H-Gly-OMe · HCl / NMM	dioxane	20	2	49	NInc-Gly-OMe (8c)
NInc-Gly-Cl (6c)	MeOH	methanol	20	1	98	NInc-Gly-OMe (8c)
NInc-Gly-Cl (6c)	C ₆ H ₁₁ NH ₂ / TEA	benzene	20	1	67	NInc-Gly-NHC ₆ H ₁₁ (10c)
Methylbenzotriazole series						
MBtcCl (1d)	MeOH	methanol	20	1	94	MBtcOMe (2d)
MBtcCl (1d)	C ₆ H ₁₁ NH ₂ / TEA	toluene	20	1	85	MBtcNHC ₆ H ₁₁ (3d)
MBtcCl (1d)	Gly	dioxane	20	120	82	MBtc-Gly-OH (4d)
MBtcCl (1d)	L-Phe	dioxane	20	24	78	MBtc-L-Phe-OH (5d)
MBtc-Gly-OH (4d)	SOCl ₂	SOCl ₂	75	1	100 ^(a)	MBtc-Gly-Cl (6d)
MBtc-Gly-Cl (6d)	MeOH	methanol	20	1	86	MBtc-Gly-OMe (8d)
MBtc-Gly-Cl (6d)	C ₆ H ₁₁ NH ₂ / TEA	toluene	20	1	74	MBtc-Gly-NHC ₆ H ₁₁ (10d)

^(a) Used for further reactions without purification.

TLC). Analogous reactions with **8a** and **8d** were completed after several hours, giving the expected dipeptide derivative in 54 % and 51 % yields, respectively.

Finally, acidolysis of the *N*-protective group from *N*-(1-azolecarbonyl)glycine or D,L-alanine cyclohexylamides **10b-d** and **11a** was studied. Amides **11a** and **10d** were completely hydrolyzed to the corresponding amino acid cyclohexylamide after 11 h at 60 °C, but **10b** and **10c** were unchanged after being heated in acidic medium for the same time, even at a higher temperature (100 °C).

N-Btc-amino acid amides¹² or peptides,¹⁵ for example, cyclohexylamide **10a** and the analogous methylbenzotriazole derivative **10d**, cyclized in an aqueous basic me-

dium (acetone or dioxane / 10 % Na₂CO₃) at room temperature to 3-cyclohexylhydantoine (**19**). The corresponding amides from indazole (**10b**) and nitroindazole (**10c**) series were unreactive and did not cyclize even after prolonged heating at 100 °C. Once again, reactivity was in good correlation with the ν(CO) shift to a higher wave number¹⁹ (see Table IV). In general, one could conclude that benzotriazole derivatives are most suitable for use in all the investigated reactions. Methylbenzotriazole derivatives were equally reactive, but the starting chloride **1d** (and its derivatives) was contaminated by 1,1'-carbonyl-bis(5-methylbenzotriazole) and purification of the products was more difficult. A review of the performed reactions is given in Table IV.

TABLE III. Characterization of azolecarboxylic acid derivatives

Compound	m.p. / °C (Lit. m.p. / °C)	Solvent for recrystallization	Formula (<i>M</i> _r)	Elemental analysis calcd. / % (found / %)			IR (KBr) ν _{max} / cm ^{−1}
				C	H	N	
Indazole series							
2b	55–58 (59–60) ^{20,25}	–	C ₉ H ₈ N ₂ O ₂ (176.18)	–	–	–	1730, 1615
3b	119–120	acetone	C ₁₄ H ₁₇ N ₃ O (243.30)	69.11 (69.10)	7.04 7.06	17.27 17.30)	3390, 2930, 2850, 1730, 1610
4b	162–164	benzene ^(a)	C ₁₀ H ₉ N ₃ O ₃ (219.19)	54.79 (54.90)	4.14 4.34	19.17 18.93)	3390, 2930, 2850, 1700, 1500
5b	119–121 ^(b)	benzene ^(a)	C ₁₇ H ₁₅ N ₃ O ₃ (309.32)	66.01 (65.92)	4.89 5.09	13.59 13.38)	3450–2400, 3390, 1725–1700, 1500
8b	96–97	acetone/H ₂ O	C ₁₁ H ₁₁ N ₃ O ₃ (233.22)	56.65 (56.97)	4.75 5.03	18.02 17.71)	3335, 1720, 1675, 1520
9b	oil ^(c)	–	C ₂₄ H ₂₁ N ₃ O ₃ (399.44)	72.17 (71.88)	5.30 5.47	10.52 10.58)	3370, 1740, 1705, 1510
10b	182–184	acetone	C ₁₆ H ₂₀ N ₄ O ₂ (300.36)	63.98 (63.86)	6.71 6.98	18.65 18.44)	3400, 2950, 2925, 1710, 1650, 1500
Nitroindazole series							
2c	177–178	acetone	C ₉ H ₇ N ₃ O ₄ (221.17)	48.87 (48.99)	3.19 2.91	19.00 19.33)	1740, 1620, 1520, 1350
3c	125–126	ethanol	C ₁₄ H ₁₆ N ₄ O ₃ (288.30)	58.32 (58.51)	5.59 5.21	19.43 19.65)	1725, 1620, 1520, 1345
4c	179–183	benzene ^(a)	C ₁₀ H ₈ N ₄ O ₅ (264.19)	45.46 (45.30)	3.05 3.17	21.20 21.31)	3500–2500, 3400, 1735– 1715, 1620, 1525, 1345
5c	68–70 ^(d)	benzene/petrol ether	C ₁₇ H ₁₄ N ₄ O ₅ (354.32)	57.63 (57.70)	3.98 4.22	15.81 15.66)	3500–2500, 1725, 1620, 1525, 1350
8c	177–178	acetone/H ₂ O	C ₁₁ H ₁₀ N ₄ O ₅ (278.22)	47.49 (47.21)	3.62 3.80	20.14 19.92)	3370, 1750, 1705, 1620, 1520, 1345, 1255
10c	224–225	^(e)	C ₁₆ H ₁₉ N ₅ O ₄ (345.35)	55.65 (55.82)	5.55 5.92	20.28 19.68)	3350, 3310, 2940, 1715, 1650, 1620, 1530, 1340
Methylbenzotriazole series							
2d	95–98	MeOH	C ₉ H ₉ N ₃ O ₂ (191.18)	56.54 (56.40)	4.74 4.93	21.98 21.68)	1753, 1450, 1265, 1057
3d	100–102	MeOH/H ₂ O	C ₁₄ H ₁₈ N ₄ O (258.32)	65.09 (65.36)	7.02 7.13	21.69 21.58)	3313, 2929, 1728, 1510
4d	150 (decomp.)	acetone/H ₂ O	C ₁₀ H ₁₀ N ₄ O ₃ (234.21)	51.28 (51.25)	4.30 4.60	23.92 23.81)	3355, 3300–2400, 1742, 1721, 1535, 1234
5d	190–194	–	C ₁₇ H ₁₆ N ₄ O ₃ (324.33)	62.95 (62.13)	4.97 4.80	17.27 16.90)	3400–2300, 1728, 1712, 1520, 1120
8d	132–134	toluene	C ₁₁ H ₁₂ N ₄ O ₃ (248.24)	53.22 (53.31)	4.87 4.99	22.57 22.20)	3364, 1754, 1730, 1526, 1216, 1099
10d	171–173	toluene	C ₁₆ H ₂₁ N ₅ O ₂ (315.37)	60.93 (60.69)	6.71 6.53	22.21 22.39)	3363, 3293, 2932, 1744, 1655, 1536

(^a) Washed with hot benzene; (^b) $[\alpha]_{\text{D}}^{20} = +18.5$ ($c = 0.96$, dioxane); (^c) $[\alpha]_{\text{D}}^{20} = +2.6$ ($c = 0.26$, chloroform); (^d) $[\alpha]_{\text{D}}^{20} = +36.5$ ($c = 1$, acetone); (^e) washed with hot acetone and ethyl acetate.

TABLE IV. Reactions of 1-azolecarboxylic acid derivatives

1-Azolecarbonyl derivative	$\nu(\text{AzC}), \nu(\text{COX})$ cm^{-1}	Reactant	Solvent	T $^{\circ}\text{C}$	t h	Yield %	Product
BtcOMe (2a)	1767	$\text{C}_6\text{H}_{11}\text{NH}_2$	benzene	80	< 0.1	67	$\text{C}_6\text{H}_{11}\text{NHCOOMe}$ (12)
IncOMe (2b)	1734	$\text{C}_6\text{H}_{11}\text{NH}_2$	benzene	80	20	63	$\text{C}_6\text{H}_{11}\text{NHCOOMe}$ (12)
NIncOMe (2c)	1740	$\text{C}_6\text{H}_{11}\text{NH}_2$	benzene	80	7	78	$\text{C}_6\text{H}_{11}\text{NHCOOMe}$ (12)
MBtcOMe (2d)	1753	$\text{C}_6\text{H}_{11}\text{NH}_2$	benzene	80	< 0.1	73	$\text{C}_6\text{H}_{11}\text{NHCOOMe}$ (12)
BtcNHC C_6H_{11} (3a)	1735	$\text{C}_6\text{H}_{11}\text{NH}_2$	benzene	80	< 0.1	98	DCU (13)
IncNHC C_6H_{11} (3b)	1705	$\text{C}_6\text{H}_{11}\text{NH}_2$	benzene/DMF	80/155	24/8	–/94	no reaction/DCU (13)
NIncNHC C_6H_{11} (3c)	1725	$\text{C}_6\text{H}_{11}\text{NH}_2$	benzene/DMF	80/155	24/6	–/95	no reaction/DCU (13)
MBtcNHC C_6H_{11} (3d)	1728	$\text{C}_6\text{H}_{11}\text{NH}_2$	benzene	80	< 0.1	92	DCU (13)
Btc-L-Phe-OH (5a)	1735, 1690	MeOH/TEA	MeOH	20	4	78	H-L-Phe-OMe (24)
Inc-L-Phe-OH (5b)	1720, 1685	MeOH/TEA	MeOH	60	7	–	no reaction
NInc-L-Phe-OH (5c)	1725, 1690	MeOH/TEA	MeOH	60	7	(a)	H-L-Phe-OMe (24)
MBtc-L-Phe-OH (5d)	1728, 1713	MeOH/TEA	MeOH	20	4	(b)	H-L-Phe-OMe (24)
Btc-Gly-OMe (8a)	1730, 1750	Z-L-Phe-OH	xylene	140	3.5	54	Z-Phe-Gly-OMe (16)
Inc-Gly-OMe (8b)	1705, 1743	Z-L-Phe-OH	xylene	140	15	(a)	Z-Phe-Gly-OMe (16)
NInc-Gly-OMe (8c)	1705, 1747	Z-L-Phe-OH	xylene	140	15	(a)	Z-Phe-Gly-OMe (16)
MBtc-Gly-OMe (8d)	1730, 1754	Z-L-Phe-OH	xylene	140	5	51	Z-Phe-Gly-OMe (16)
Btc-D,L-Ala-NHC C_6H_{11} (11a)	1740, 1660	H^+	acetone / 5 % HCl	60	11	86	H-D,L-Ala-NHC C_6H_{11} (18)
Inc-Gly-NHC C_6H_{11} (10b)	1710, 1625	H^+	dioxane / 5 % HCl	100	11	–	no reaction
NInc-Gly-NHC C_6H_{11} (10c)	1715, 1645	H^+	dioxane / 5 % HCl	100	11	–	no reaction
MBtc-Gly-NHC C_6H_{11} (10d)	1744, 1655	H^+	acetone / 5 % HCl	60	11	(b)	H-Gly-NHC C_6H_{11} (17)
Btc-Gly-NHC C_6H_{11} (10a)	1740, 1650	Na_2CO_3	acetone / H_2O	20	0.35	56	3-cyclohexylhydantoine (19)
Inc-Gly-NHC C_6H_{11} (10b)	1710, 1625	Na_2CO_3	dioxane / H_2O	100	5	–	no reaction
NInc-Gly-NHC C_6H_{11} (10c)	1715, 1645	Na_2CO_3	dioxane / H_2O	100	5	–	no reaction
MBtc-Gly-NHC C_6H_{11} (10d)	1744, 1655	Na_2CO_3	acetone / H_2O	20	0.35	(b)	3-cyclohexylhydantoine (19)

(a) The reaction proceeded partially; product was not isolated.

(b) The reaction proceeded completely (TLC); product was not isolated.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on an FT-IR Perkin Elmer Paragon 500 spectrometer (Perkin Elmer, UK). ^1H NMR spectra were recorded on a Varian Gemini 300 spectrometer (Varian, USA), operating at 300 MHz. Samples were measured in $\text{DMSO}-d_6$ solutions at $20\text{ }^{\circ}\text{C}$ in 5-mm NMR tubes. Chemical shifts in ppm were referred to TMS. Specific rotation data were taken on an Opton polarimeter. For thin-layer chromatography, silica gel sheets Kieselgel 60 F254 Merck were used. Solvent systems were dichloromethane/methanol in the ratio 9:1, 7:3 or 1:1, 2-butanol/formic acid/water 75:15:10 and dioxane/water 9:1. Column chromatography was performed on silica gel 0.063–0.200 mm, using benzene/ethyl acetate 1:1 as eluent.

Benzotriazole derivatives were prepared according to published procedures: BtcNHC C_6H_{11} (**3a**),² Btc-L-Phe-OH (**5a**),¹¹ Btc-Gly-OMe (**8a**),¹⁵ Btc-Gly-NHC C_6H_{11} (**10a**),¹² Btc-D,L-Ala-NHC C_6H_{11} (**11a**).¹² Methyl 1-benzotriazolecarboxylate (BtcOMe, **2a**) was prepared analogously to the

previously published ethyl ester.¹ Azoles and triphosgene were purchased from Aldrich (USA). All solvents were previously dried and amines were distilled prior to use.

Benzotriazole Series

1-Benzotriazolecarbonyl Chloride (BtcCl, 1a). – a) A solution of benzotriazole (0.48 g, 4 mmol) and TEA (0.43 g, 4.3 mmol) in dioxane (5 ml) was added dropwise to a solution of triphosgene (0.42 g, 1.4 mmol) in dioxane (5 ml). The reaction mixture was stirred for 1 h at room temperature. Precipitated TEA · HCl was filtered off and the mother liquor was evaporated.

b) A solution of benzotriazole (0.48 g, 4 mmol) and triphosgene (0.50 g, 1.7 mmol) in toluene (10 ml) was refluxed for 3 h. The solvent was evaporated in vacuum and the obtained crude product was used in further reactions without purification.

IR spectrum of **1a** was identical to the spectrum of the product prepared from phosgene solution in toluene.⁹

Indazole Series (Tables II and III)

1-Indazolecarbonyl Chloride (IncCl, 1b). – A solution of indazole (1.18 g, 10 mmol) in toluene (13 ml) and 20 % solution of phosgene in toluene (13 ml) was heated at 90 °C for 1 h. The solvent was evaporated in vacuum. The obtained crude product was used in further reactions without purification. Yield: 1.81 g (100 %). m.p. 72–74 °C. Lit. m.p.²⁰ 73–74 °C.

Methyl 1-Indazolecarboxylate (IncOMe, 2b). – A solution of IncCl (**1b**) (1.81 g, 10 mmol) in methanol (3 ml) was stirred at room temperature for 1 h and then evaporated in vacuum. The crude product **2b** was obtained in a quantitative yield (1.72 g, 98 %). m.p. 56–58 °C. Lit. m.p.^{20,25} 59–60 °C.

1-Indazolecarboxylic Acid Cyclohexylamide (IncNHC₆H₁₁, 3b). – To a solution of IncCl (**1b**) (1.26 g, 7 mmol) and TEA (0.71 g, 7 mmol) in benzene (35 ml), a solution of cyclohexylamine (0.69 g, 7 mmol) in benzene (95 ml) was slowly added. The reaction mixture was stirred at room temperature for 1 h and extracted 3 times with water. The organic layer was dried over sodium sulphate and the solvent was evaporated. The crude product (1.60 g, 94 %) **3b** was recrystallized from acetone. m.p. 119–120 °C.

N-(1-Indazolecarbonyl)glycine (Inc-Gly-OH, 4b). – To a suspension of glycine (4.50 g, 60 mmol) in dioxane (80 ml), a solution of IncCl (**1b**) (5.42 g, 30 mmol) in dioxane (70 ml) was slowly added. The reaction mixture was stirred at room temperature for 20 h. Glycine hydrochloride was filtered off and the mother liquor was evaporated in vacuum. The obtained product **4b** was treated with dry benzene and filtered off (5.42 g, 82 %). m.p. 162–164 °C.

N-(1-Indazolecarbonyl)-L-phenylalanine (Inc-L-Phe-OH, 5b). – Analogous procedure to that for **4b**. The used amounts of reactants and solvent were: L-phenylalanine (3.30 g, 20 mmol), IncCl (**1b**) (1.81 g, 10 mmol), dioxane (50 ml). Yield: 2.78 g (90 %) of **5b**. m.p. 119–121 °C.

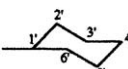
N-(1-Indazolecarbonyl)glycine Chloride (Inc-Gly-Cl, 6b). – Inc-Gly-OH (**4b**) (1.10 g, 5 mmol) was suspended in thionyl chloride (25 ml). The solution was stirred at room temperature for 19 h, evaporated and triturated several times with a small quantity of benzene. The obtained crude product was used in further reactions without purification.

N-(1-Indazolecarbonyl)-L-phenylalanine Chloride (Inc-L-Phe-Cl, 7b). – Analogous procedure to that for **6b**.

N-(1-Indazolecarbonyl)glycine Methyl Ester (Inc-Gly-OMe, 8b). – To a suspension of IncCl (**1b**) (0.72 g, 4 mmol) and glycine methyl ester hydrochloride (**14**) (0.50 g, 4 mmol) in dioxane (12 ml), a solution of NMM (1.01 g, 10 mmol) in dioxane (8 ml) was added dropwise. The reaction mixture was stirred at room temperature for 2 h and evaporated in vacuum. The obtained crude product **8b** was purified by column chromatography (eluent benzene/ethyl acetate 1:1). Yield: 0.59 g (63 %). m.p. 96–97 °C.

N-(1-Indazolecarbonyl)-L-phenylalanine Benzyl Ester (Inc-L-Phe-OBzl, 9b). – a) Analogous procedure to that for **8b**. The used amounts of reactants and solvent were: IncCl (**1b**) (0.09 g, 0.5 mmol), L-phenylalanine benzyl ester hydrochloride (**15**) (0.15 g, 0.5 mmol), NMM (0.10 g, 1 mmol), dioxane (5 ml). Yield: 0.08 g (41 %) of **9b**. $[\alpha]_D^{20} = +2.6^\circ$ ($c = 0.24$, CHCl₃).

TABLE V. ¹H NMR spectral data of some MBtc-derivatives in DMSO-d₆, δ / ppm

Atom	R (compound)			
	OCH ₃ (2d)	NHC ₆ H ₁₁ (3d)	NHCHCOOH (4d)	NHCHCOOCH ₃ (8d)
H-4	7.87, m, 1H	7.98, s, 1H	7.98, s, 1H	7.97, s, 1H
CH ₃ -Ar	2.55, s, 3H	2.53, s, 3H	2.53, s, 3H	2.53, s, 3H
H-6	7.41, dd, 1H, ³ J = 8.5 Hz, ⁴ J = 1.1 Hz	7.75, dd, 1H, ³ J = 8.5 Hz, ⁴ J = 1.2 Hz	7.39, dd, 1H, ³ J = 8.5 Hz, ⁴ J = 1.1 Hz	7.39, d, 1H, ³ J = 8.5 Hz
H-7	8.09, d, 1H, ³ J = 8.5 Hz	8.05, d, 1H, ³ J = 8.5 Hz	8.07, t, 1H, ³ J = 8.9 Hz	8.08, d, 1H, ³ J = 8.6 Hz
COOH	–	–	12.92, s, 1H	–
CH ₃ -ester	4.16, s, 3H	–	–	3.71, s, 3H
NH	–	8.98, t, 1H, ³ J = 7.7 Hz	9.41, dd, 1H, ³ J = 5.9 Hz	9.54, t, 1H, ³ J = 5.4 Hz
CH ₂	–	–	4.04, d, 2H, ³ J = 6.0 Hz	4.15, d, 2H, ³ J = 5.9 Hz
	–	3.82–3.69, m, 1H, H1', 1.05–1.91, m, 10H, H2'–6'	–	–

b) A solution of TEA (0.30 g, 3 mmol) and benzyl alcohol (0.32 g, 3 mmol) was added dropwise to a solution of Inc-L-Phe-Cl (**5e**) (0.98 g, 3 mmol) in benzene (30 ml). The reaction mixture was stirred at room temperature for 45 min and extracted 3 times with water. The organic layer was dried over sodium sulphate and evaporated to give **9b**. Yield: 0.97 g (81 %). The crude product was purified by column chromatography.

N-(1-Indazolecarbonyl)glycine Cyclohexylamide (Inc-Gly-NHC₆H₁₁, **10b**). – A solution of cyclohexylamine (0.50 g, 5 mmol) and TEA (0.51 g, 5 mmol) in benzene (15 ml) was added dropwise to a solution of Inc-Gly-Cl (**6b**) (1.19 g, 5 mmol) in benzene (60 ml). The reaction mixture was stirred at room temperature for 45 min and evaporated in vacuum. The residue was mixed with 50 ml water. The insoluble sticky product was filtered off, dissolved in chloroform and extracted two times with a 5 % HCl solution. The organic layer was dried over sodium sulphate and evaporated to give **10b**. Yield: 1.25 g (83 %). The sample for analysis was washed with benzene and recrystallized from acetone. m.p. 182–184 °C.

Nitroindazole Series (Tables II and III)

5-Nitro-1-indazolecarbonyl Acid Chloride (NIncCl, **1c**). – Analogous procedure to that for **1b**. The used amounts of

reactants and solvents were: 5-nitroindazole (0.49 g, 3 mmol), 20 % solution of phosgene in toluene (5 ml), toluene (5 ml). Yield: 0.64 g (94 %). m.p. 144–145 °C.

Methyl 5-Nitro-1-indazolecarboxylate (NIncOMe, **2c**). – A solution of NIncCl (**1c**) (1.13 g, 5 mmol) in methanol (7 ml) was stirred at room temperature for 1 h. Precipitated product **2c** was filtered off (0.74 g, 67 %). An additional amount of **2c** was isolated from the mother liquor (0.13 g, 12 %). m.p. 177–178 °C.

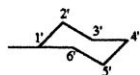
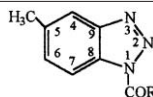
5-Nitro-1-indazolecarboxylic Acid Cyclohexylamide (NInc-NHC₆H₁₁, **3c**). – Analogous procedure to that for **3b**, but with a prolonged reaction time (2.5 h). The used amounts of reactants and solvents were: NIncCl (**1c**) (0.99 g, 4.4 mmol), TEA (0.49 g, 4.4 mmol), cyclohexylamine (0.44 g, 4.4 mmol), benzene (80 ml). Yield: 1.00 g (79 %). m.p. 125–126 °C.

N-(5-Nitro-1-indazolecarbonyl)glycine (NInc-Gly-OH, **4c**). – Analogous procedure, the same scale and quantitative yield as for **4b**. m.p. 179–183 °C.

N-(5-Nitro-1-indazolecarbonyl)-L-phenylalanine (NInc-L-Phe-OH, **5c**). – Analogous procedure to that for **4b**. The used amounts of reactants were: L-phenylalanine (0.94 g, 5.7 mmol), NIncCl (**1c**) (0.63 g, 2.8 mmol), dioxane (15 ml). Yield: 0.70 g (71 %). m.p. 68–70 °C.

TABLE VI. ¹³C NMR spectral data of some MBtc-derivatives in DMSO-d₆, δ / ppm

Atom	R (compound)			
	OCH ₃ (2d)	NHC ₆ H ₁₁ (3d)	NHCHCOOH (4d)	NHCHCOOCH ₃ (8d)
C-4	113.22	113.28	113.16	113.14
C-5	132.15	132.36	132.18	132.58
CH ₃ (at C5)	22.09	22.12	22.11	22.10
C-6	128.32	127.92	128.14	128.16
C-7	120.04	119.70	119.85	119.87
C-8	141.65	140.77	141.22	141.31
C-9	144.28	146.51	146.55	146.55
CH ₂	–	–	42.23	42.21
COOH (CH ₃)	149.48	–	171.09	170.20
CH ₃ -ester	55.83	–	–	52.58
CONH		148.75	149.97	150.13
		50.33 (C1')		
		25.43		
		25.52		
		32.48		



N-(5-Nitro-1-indazolecarbonyl)glycine Chloride (NInc-Gly-Cl, **6c**). – Analogous procedure to that for **6b**.

N-(5-Nitro-1-indazolecarbonyl)-L-phenylalanine Chloride (NInc-L-Phe-Cl, **7c**). – Analogous procedure to that for **6b**.

N-(5-Nitro-1-indazolecarbonyl)glycine Methyl Ester (NInc-Gly-OMe, **8c**). – a) A suspension of NInc-Gly-Cl (**6c**) (0.73 g, 2.6 mmol) in methanol (20 ml) was refluxed for 1 h and then stirred at room temperature for 17 h. The precipitated product **8c** was filtered off (0.51 g, 70 %). An additional amount of the product was obtained from the mother liquor (0.10 g, 14 %). The sample for analysis was recrystallized from acetone/H₂O. m.p. 177–178 °C.

b) Analogous procedure to that for **8b**. The used amounts of reactants and solvents were: NIncCl (**1c**) (0.59 g, 2.6 mmol), glycine methyl ester hydrochloride (**14**) (0.33 g, 2.6 mmol), NMM (0.61 g, 6 mmol), dioxane (25 ml). Yield after column chromatography: 0.82 g (49 %).

N-(5-Nitro-1-indazolecarbonyl)-glycine Cyclohexylamide (NInc-Gly-NHC₆H₁₁, **10c**). – A solution of cyclohexylamine (0.20 g, 2 mmol) and TEA (0.20 g, 2 mmol) in benzene (10 ml) was added dropwise to a mixture of NInc-Gly-Cl (**6c**) (0.57 g, 2 mmol) in benzene (35 ml). The reaction mixture was stirred at room temperature for 3 h. The precipitated product **9c** was filtered off and washed with water. Yield: 0.46 g (67 %). The sample for analysis was washed with hot acetone and ethyl acetate. m.p. 224–225 °C.

Methylbenzotriazole Series (Tables II, III, V and VI)

5-Methyl-1-benzotriazolecarbonyl Chloride (MBtcCl, **1d**). – a) Analogous procedure to that for **1b** from 5-methylbenzotriazole (1.33 g, 10 mmol) in toluene (20 ml) and 20 % solution of phosgene in toluene (10 ml). The product was used in the synthesis of **2d** without further purification.

b) Analogous procedure to that for **1a** (experiment a) from 5-methylbenzotriazole (1.33 g, 10 mmol), triphosgene (1.10 g, 3.7 mmol) and TEA (1.01 g, 10 mmol) in dioxane (15 + 15 ml). The product was used in the synthesis of **3d** without further purification.

Methyl 5-Methyl-1-benzotriazolecarboxylate (MBtcOMe, **2d**). – A solution of MBtcCl (**1d**) (1.96 g, 10 mmol) in methanol (10 ml) was stirred at room temperature for 1 h and then evaporated in vacuum. The crude product **2d** was recrystallized from acetone and 1 % hydrochloric acid. Yield: 1.80 g (94 %). m.p. 95–98 °C.

5-Methyl-1-benzotriazolecarboxylic Acid Cyclohexylamide (MBtcNHC₆H₁₁, **3d**). – A solution of cyclohexylamine (0.99 g, 10 mmol) in toluene (40 ml) was slowly added to a solution of MBtcCl (**1d**) (1.96 g, 10 mmol) and TEA (1.01 g, 10 mmol) in toluene (40 ml). The reaction mixture was stirred at room temperature for 1 h and extracted 3 times with 1 % hydrochloric acid and water. The organic layer was dried over sodium sulphate and evaporated. The crude product **3d** (2.03 g, 79 %) was recrystallized from methanol/water. m.p. 100–102 °C.

N-(5-Methyl-1-benzotriazolecarbonyl)glycine (MBtc-Gly-OH, **4d**). – To a suspension of glycine (3.00 g, 40 mmol) in dioxane (30 ml), a solution of MBtcCl (**1d**) (3.83 g, 20 mmol) in dioxane (30 ml) was added. The reaction mixture was stirred at room temperature for 3 days. Glycine hydrochloride was filtered off and the mother liquor was evaporated in vacuum. The obtained oil product **4d** was treated with dry toluene, filtered off and washed with petrol ether. Yield: 3.33 g (71 %). m.p. ca. 150 °C (decomp.).

N-(5-Methyl-1-benzotriazolecarbonyl)-L-phenylalanine (MBtc-L-Phe-OH, **5d**). – Analogous procedure to that for **4b**. The used amounts of reactants and solvent were: L-phenylalanine (3.30 g, 20 mmol), MBtcCl (**1d**) (1.96 g, 10 mmol), dioxane (60 ml). Reaction time: 3 days. According to TLC, the gummy product **5d** contained small amounts of amino acid and 5-methylbenzotriazole. Repeated purification from toluene/petrol ether was partially successful. Yield: 0.88 g (27 %) of **5d**. After a long treatment in high vacuum, an amorphous solid was obtained. m.p. 190–194 °C (sint. at 120 °C).

N-(5-Methyl-1-benzotriazolecarbonyl)glycine Chloride (MBtc-Gly-Cl, **6d**). – Analogous procedure to that for **6b**. The used amounts of reactants: **4d** (2.34 g, 10 mmol) and thionyl chloride (25 ml). The product was used in the synthesis of **8d** and **10d** without purification.

N-(5-Methyl-1-benzotriazolecarbonyl)glycine Methyl Ester (MBtc-Gly-OMe, **8d**). – MBtc-L-Phe-Cl (**6d**) (1.26 g, 5 mmol) was dissolved in 10 ml methanol. The reaction mixture was evaporated after 1 hour. The residue was dissolved in ethyl acetate and extracted with 3 % hydrochloric acid and water, dried over sodium sulphate and evaporated. Yield: 1.07 g (86 %) of an oil product, which slowly crystallized. m.p. 132–134 °C.

N-(5-Methyl-1-benzotriazolecarbonyl)glycine Cyclohexylamide (MBtc-Gly-NHC₆H₁₁, **10d**). – A solution of cyclohexylamine (0.50 g, 5 mmol) and TEA (0.51 g, 5 mmol) in toluene (15 ml) was added dropwise to a solution of MBtc-Gly-Cl (**6d**) (1.26 g, 5 mmol) in toluene (50 ml) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and evaporated in vacuum. The residue was dissolved in ethyl acetate and extracted with 5 % HCl solution and water. The organic layer was dried over sodium sulphate and evaporated to give **10d**. Yield: 1.15 g (73 %). The sample for analysis was washed with benzene and recrystallized from toluene. m.p. 171–173 °C.

Reactions of 1-Azolecarboxylic Acid Derivatives (Table IV)

Reactions of Methyl 1-Azolecarboxylates **2a-d** with Cyclohexylamine. Preparation of Methyl N-Cyclohexylcarbamate (**12**). – A mixture of **2a**, **2b**, **2c** or **2d** (3 mmol) and cyclohexylamine (6 mmol) in benzene (15 ml) was refluxed (Table IV). After cooling at room temperature, azole cyclohexylamine salt was filtered off and the mother liquor was extracted several times with a 1 % HCl solution and then with water. The organic layer

was dried over anhydrous sodium sulphate and evaporated in vacuum. The crude product **10** was recrystallized from methanol/H₂O or purified on a silica gel column (benzene/ethyl acetate 1:1). m.p. 69–72 °C. Lit.³¹ m.p. 72–75 °C.

Reactions of 1-Azolecarboxamides 3a–d with Cyclohexylamine. *Preparation of 1,3-Dicyclohexylurea (DCU, 13).* – A mixture of **3a**, **3b**, **3c** or **3d** (1 mmol) and cyclohexylamine (6 mmol) in a solvent (5 ml) was stirred under the reaction conditions given in Table IV. Only reactants **3a** and **3d** gave urea **13** at 80 °C. Amides **3b** and **3c** gave the urea if the reaction was run at 155 °C. After cooling at room temperature, DCU was filtered off and compared by TLC, IR and m.p. with the sample urea (Aldrich).

Thermal Dissociation of 3b and 3c. – A solution of **3b** or **3c** (1 g) in DMF (30 ml) was distilled to a flask containing 1 ml cyclohexylamine in 10 ml DMF. After evaporation of the solvent and treatment with ether, DCU was isolated.

Reactions of N-(1-Azolecarbonyl)-L-phenylalanine 5a–d with Methanol. *Preparation of L-Phenylalanine Methyl Ester (H-L-Phe-OMe, 24).* – A mixture of **5a**, **5b**, **5c** or **5d** (1 mmol) and TEA (0.5 ml) in methanol (10 ml) was stirred under the reaction conditions given in Table IV. Compound **5b** did not react, **5c** reacted only partially while **5a** and **5d** reacted under mild reaction conditions and gave L-phenylalanine methyl ester (**24**). Product **24** (prepared from **5a**) was isolated as hydrochloride salt. m.p. 154–156 °C. Lit.¹⁴ m.p. 156–158 °C.

Reactions of N-(1-Azolecarbonyl)glycine Methyl Esters 8a–d with N-Benzyloxycarbonyl-L-phenylalanine (Z-L-Phe-OH). *Preparation of N-Benzyloxycarbonyl-L-phenylalanyl-glycine Methyl Ester (Z-L-Phe-Gly-OMe, 16).* – A mixture of **8a**, **8b**, **8c** or **8d** (1 mmol) and Z-L-Phe-OH (1 mmol) was refluxed in xylene (10 ml) (Table IV). Reactions with **8b** and **8c** did not end even after 15 h (TLC control), while the reactions with **8a** and **8d** finished after 3.5 and 5 h, respectively, yielding Z-L-Phe-Gly-OMe (**16**). The solvent from the completed reactions was evaporated under vacuum and replaced with ether. The majority of dipeptide ester **16** precipitated (54 and 51 %, respectively), while the corresponding azole by-product was dissolved. An additional amount (20–25 %) of **16** could be isolated from the mother liquor. m.p. 118–120 °C. Lit.³² m.p. 122–123 °C.

Acidolysis of the Protective Group from N-(1-Azolecarbonyl)glycine (10b–d) or D,L-Alanine (11a) Cyclohexylamides. *Preparation of Glycine (17) and Alanine (18) Cyclohexylamides.* – A sample of **11a**, **10b**, **10c** or **10d** (20 mg) in a dioxane/5 % HCl (1:1) mixture (5 ml) was heated under the conditions given in Table IV. No hydrolysis was observed in compounds **10b** and **10c** during 11 h, while compounds **11a** and **10d** were hydrolyzed completely during the same time span even at lower temperature. Cyclohexylamide hydrochloride (**18**) was isolated as the product.¹⁵

Cyclization of N-(1-Azolecarbonyl)glycine Cyclohexylamides 10a–d. *Preparation of 3-Cyclohexylhydantoine (19).* – To a solution of **10a** or **10d** (1 mmol) in acetone (30 ml) or **10b** or **10c** (1 mmol) in dioxane (30 ml), 10 % Na₂CO₃ (3 ml)

solution was added. The first two reactions gave 3-cyclohexylhydantoine (**19**) after a short stirring at room temperature while the second two failed to cyclize, even after prolonged reflux. The hydantoine was precipitated after evaporation of acetone and addition of 10 ml water. TLC, IR and m.p. of the product were equal to those of the hydantoine sample prepared previously.¹²

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ABBREVIATIONS

AA – amino acid; AzH – azole; Bzl – benzyl; Btc – 1-benzotriazolecarbonyl; BtH – benzotriazole; CA – cyclohexylamine; DCU – 1,3-dicyclohexylurea; DMF – *N,N*-dimethylformamide; Inc – indazolecarbonyl; InH – indazole; MBtc – 5-methylbenzotriazolecarbonyl; MBtH – 5-methylbenzotriazole; Me – methyl; NInc – 5-nitro-1-indazolecarbonyl; NInH – 5-nitroindazole; NMM – *N*-methylmorpholine; TEA – triethylamine; Z – benzyloxycarbonyl.

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SAŽETAK

Sinteza i reakcije derivata nekih azolkarboksilnih kiselina

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Proučavane su reakcije nekoliko azola s fosgenom ili trifosgenom. Osim ranije opisane reakcije s benzotriazolom, pokazalo se da samo indazol, 5-nitroindazol i 5-metilbenzotriazol daju odgovarajuće 1-azolkarbonil-kloride **1a-d**. Slabo kiseli azoli (imidazol, pirazol, 1,2,3-triazol, 1,2,4-triazol, benzimidazol) ne daju stabilne kiselinske kloride, dok jako kiseli azoli kao što su tetrazol i 4,5,6,7-tetraklorbenzotriazol uopće ne reagiraju. Kloridi **1b-d** reagiraju s alkoholima, aminima, aminokiselinama i njihovim esterima kao i ranije istraženi 1-benzotriazolkarbonil-klorid (**1a**), dajući estere (**2**) ili amide (**3**) 1-azolkarboksilnih kiselina ili *N*-(1-azolkarbonil)aminokiseline (**4**, **5**), njihove estere (**8**, **9**) ili amide (**10**, **11**). Međutim, primijećena je značajna razlika u reaktivnosti derivata azola **2–11** s aminima, alkoholima, *N*-zaštićenim aminokiselinama, kiselinama i bazama. Derivati benzotriazola i metilbenzotriazola mnogo su reaktivniji od derivata indazola ili nitroindazola. Povećana reaktivnost bila je u korelaciji s pomakom apsopijske vrpce karbonilne skupine u IR području prema većim valnim brojevima.